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| 10/045,400      | 11/29/2001  | Chulso Moon          | P-CAN 1004          | 4431             |

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EXAMINER

YU, MISOOK

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/045,400

**Applicant(s)**

MOON ET AL.

**Examiner**

MISOOK YU, Ph.D.

**Art Unit**

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 and 43-57 is/are pending in the application.
- 4a) Of the above claim(s) 57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 43-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 11/08/04.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election of group I in the reply filed on 10/20/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 43-57 are new. Claim 57, drawn to assessing whether a test compound is useful is a different invention. The elected invention and the invention claimed in claim 57 are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to different methods with different reagents for different purposes. Group I involves searching of whether lower expression of DAP-kinase is indication of lung cancer, while claim 57 is drawn to screening a compound.

Claim 57 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

### ***Specification***

The disclosure is objected to because of the following informalities: DNA sequences in Fig. 3 and 4 are identified with Genbank accession numbers instead of SEQ ID NOs. Adding the corresponding SEQ ID NOs in the figure legends at page 6 of the specification would obviate this objection.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2 my 1-13-04  
Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: conclusion step linking how the assessing methylation of the gene in the active step is used for the purpose set out in the preamble of the method claim. By amending the claim similar to the claim construction of claim 53 would obviate this rejection. .

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 43, and 45, and 48-54 are rejected under 35 U.S.C. 102(a) as being anticipated by Tang et al., (IDS, 9/20/2000, Journal of the National Cancer Institute, vol. 92, pages 1511-1516).

The claims are interpreted as drawn to method of diagnosing (claims 1, 43, 45, 48-51) non-small cell lung cancer (NSCLC), assessing NSCLC tumorigenesis at an

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early stage of NSCLC (claim 52), or assessing aggressiveness of a NSCLC (claims 53) in a human patient, wherein the active step of the claimed method comprises assessing the expression of DAP-kinase gene and detection of lower expression of the gene is indicative of NSCLC, or bad outcome for the patient, wherein the expression is assessed in vitro using cells obtained from the human (claim 43), wherein the cells are epithelial cells (claim 45), wherein the expression of the gene is assessed by assessing methylation of the gene (claim 48), wherein methylation of the promoter CpG region is assessed (claim 49), wherein a first oligonucleotide hybridizing specifically to a methylated form of the gene is used (claim 50), wherein a portion of the gene is amplified by a PCR using two primers (claim 51), wherein the tumor in claim 53 is a diagnostic stage I NSCLC tumor (claim 54).

Tang et al., teach at page 1511-1512 under the heading "SUBJECTS and METHODS" a method of assessing the expression of DAP-kinase gene from epithelia cells of pathologic stage I NSCLC (note the definition of "carcinoma" Merriam-Webster Online Dictionary downloaded on 1/13/2005 (from the url...www.m-w.com) indicates that carcinoma cells of NSCLC are epithelia cells) obtained from a human patient using PCR in vitro, wherein the expression of the gene is assessed by assessing methylation in the promoter of CpG region of the DAP kinase using "specific primers for either the methylated or the unmethylated DAP kinase promoter" by amplifying a portion of the gene by a PCR using two primers (note page 1512 1<sup>st</sup> column, under the subheading "Methylation-specific polymerase chain reaction (PCR)". Thus, Tang et al., teach all the technical aspects of assessing DAP gene expression.

As for conclusion part of the instantly claimed invention, Tang et al., teach that lower expression of DAP kinase due to the hypermethylation is one of the biomarker for NSCLC, and NSCLC tumorigenesis at an early stage of NSCLC i.e. "stage I", and hypermethylation is associated with aggressiveness of a NSCLC, i.e. survival rate is poorer (note Fig. 2), and the abstract, i.e. "Hypermethylation of the DAP kinase promoter was found in 59 (44%) of the 135 tumors. Patients whose tumors exhibited such hypermethylation had a statistically significantly poorer probability of overall survival at 5 years after surgery than those without such hypermethylation (.46 versus .68;  $P = .007$ ). Moreover, the groups with and without hypermethylation of the DAP kinase promoter showed a striking difference in the probability of disease-specific survival; i.e., among people who died of lung cancer-related causes specifically, the probability of 5-year survival was .56 for those with such hypermethylation and .92 for those without it ( $P < .001$ ). Multivariate analysis indicated that hypermethylation of the DAP kinase promoter is the only independent predictor for disease-specific survival among clinical and histologic parameters tested. CONCLUSIONS: Hypermethylation of the DAP kinase promoter is a common abnormality in early-stage NSCLC. This abnormality is strongly associated with survival, suggesting that DAP kinase plays an important role in determining the biologic aggressiveness of early-stage NSCLC."

Thus, Tang et al., anticipates the instant claims 1, 43, and 45, and 48-54.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al., (cited above) in view of Field et al., (IDS, Micorsatellite instability in non-small-cell lung cancer and bronchial lavage specimens, Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, meeting abstract).

Claims 1, 43, and 44 are interpreted as drawn to method of diagnosing NSCLC by assessing DAP kinase expression in vitro in cells obtained from a human bronchial lavage.

Tang et al., teach method diagnosing NSCLC by assessing DAP kinase expression in vitro in cells obtained from a human patient. See 102 (b) rejection above for further details of what Tang et al., teach.

Tang et al., do not teach "bronchial lavage" in the instant claim 44.

However, Field et al., teach that bronchial lavage specimens contain material that could be used for detection of certain DNA status, in this case the status of "microsatellite".

Therefore, it would have been obvious for one of ordinary skill to use the DNA in “bronchial lavage” specimen instead of the lung biopsy sample of Tang et al., as the source of the template in the PCR reaction in order to access the methylation status of DAP kinase with reasonable expectation of success. One of skill would be motivated to use bronchial lavage specimen because lung biopsy involves cutting while lavage involves washing and washing appears to be less invasive procedure.

Claims 1, 46, 47, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al., (cited above).

Claims 1, 46, 47, 55, and 56 are interpreted as drawn to method of using DAP kinase as an early biomarker for NSCLC before a human patient exhibits the various clinical symptoms listed in the instant claim 47, wherein claim 55 further comprises selecting more aggressive treatment if higher degree of methylation in DAP kinase is detected.

Tang et al., teach the irrefutable link between hypermethylation of DAP kinase promoter and NSCLC, as well as the reagents and techniques necessary to assess methylation status of DAP kinase as discussed above in the 102(b) rejection. Tang et al., teach at the introduction, right after the abstract that “advances in the early detection of lung cancer” lead to early detection of lung cancer, and with these advances in the early detection of lung cancer, more patients with lung cancers will be diagnosed at early stages. This statement suggests that the reason for undertaking the study in Tang et al., is to use DAP kinase as the early marker for the NSCLC and in order to use early

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biomarkers and validation of the DAP kinase against the acknowledged disease end points was necessary. Based on the 135 prospective population trials with the pathologic stage I NSCLC, Tang et al., teach the irrefutable link between hypermethylation of DAP kinase promoter and NSCLC. Therefore, one of ordinary skill would be motivated to screen the high-risk groups of people such as smokers for NSCLC using the validated marker disclosed in Tang et al. Thus, it would have been obvious to use DAP kinase as an early biomarker for screening NSCLC patients before a human patient exhibits the various clinical symptoms listed in the instant claim 47 with a reasonable expectation of success since Tang et al., already established the irrefutable link between hypermethylation of DAP kinase promoter and “the biologic aggressiveness of NSCLC” (note the last line of the abstract).

As for claim 55, Tang et al., also in the abstract teach “the current clinical means cannot predict whether a patient may be cured by surgical treatment alone or will require additional and more aggressive treatment to improve the long-term survival. It is, therefore, desirable strategies be developed to augment the current NSCLC staging system for better classification of early stage disease. Subsequently, better treatments might be devised for patients with a high risk of disease or metastasis in addition to complete surgical resection of primary tumors.” (note middle column, 2<sup>nd</sup> paragraph at page 1511).

Therefore it would have been obvious to select more aggressive treatment for those patients if a higher degree of methylation is detected since Tang et al., at Fig. 2 teach the long-term survival rate is decreased with the hypermethylation in DAP kinase.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.  
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Art Unit 1642



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